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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

ATTY.'S DOCKET: **GABIZON=1**

In re Application of:	Art Unit: 1651
Albert GABIZON et al	Examiner: J. Weber
Appln. No.: 09/555,674	Washington, D.C.
I.A. Appln No: PCT/IL98/00586 I.A. Date: December 1, 1998	
Nationalized: August 3, 2000	Confirmation No. 8870
For: COMBINED CHEMO-IMMUNOTHERAPY WITH LIPOSOMAL DRUGS AND...	March 18, 2003

REPLY: REQUEST FOR RECONSIDERATION

Honorable Commissioner for Patents
Washington, D.C. 20231

Sir:

The Office Action mailed December 18, 2002, and the prior art applied therein have been carefully reviewed. Taking into account the examiner's amendment, entered prior to reopening of prosecution, in which a number of claims were deleted as redundant, the claims in the application are now claims 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90 and 92, and these claims define patentable subject matter under §§102 and 103 and should be allowed. Applicants therefore respectfully request favorable consideration and early formal allowance.

Applicants request that the PTO change the attorney docket number for this case to **"GABIZON=1"** as indicated above.

Claims 54, 56, 58, 60, 62, 64, 66, 68 and 70 have been allowed. Applicants accordingly understand that these claims are deemed by the PTO to define novel and unobvious subject matter under §§102 and 103.

Claims 72, 74, 76, 78, 80, 82, 84, 86, 88, 90 and 92 have been rejected under §103 as obvious from Ostro EP 546,951 (Ostro), in view of the Kedar et al publication of 1994, citation AN (Kedar). This rejection is respectfully traversed.

The PTO asserts in the rejection that Ostro discloses a combination therapy for treating neoplasms comprising administration of liposomes or MLV encapsulated antineoplastic drug followed by administration of hematopoietic cell stimulating cytokine beginning on the fourth day after drug administration (example 3).

Further stated in the rejection is that Kedar discloses advantages for the therapeutic treatment of neoplasms of administering cytokines in MLVs compared to free cytokine in solution. Thus, according to the rejection, a person of ordinary skill in the art would have

been motivated to substitute the MLV encapsulated cytokines of Kedar for non-encapsulated cytokines in the method of Ostro.

However, as also admitted by the PTO in the rejection, Ostro does not teach or suggest the administration of the cytokine by the use of MLVs, and, contrary to the PTO's position, Kedar also does not teach the use of this specific vehicle and its advantages over other liposomal vehicles. Kedar describes the effect of free IL-2, IL-2 encapsulated in **small unilamellar liposomes** (SUVs, (SSL-IL-2)) and PEGylated IL-2 on hematologic parameters (e.g. level of WBC and platelets) and the effect on tumors of combining these three preparations with chemotherapy. This is quite an importantly difference from the present invention which makes use of **multilamellar liposomes** (MLVs).

Thus, there is a great difference between small unilamellar liposomes (SUVs) and MLVs. First, SUVs have a mean diameter of 0.05-0.06 μm while MLVs are larger structures, with a mean diameter of 1.5 μm. In addition to their size, SUVs and MLVs are different in their biofate, tissue distribution, etc.

In particular, MLV-encalsulated cytokines enable the delivery of the cytokine to the reticuloendothelial

system (RES, also referred to as the mononuclear phagocytic system) and to the lymphoid tissue draining the area of injection, where it exerts its effect as an immunostimulatory, but it is clearly inefficient for the systemic delivery of the cytokine to the tumor site due to its large size.

Against this, when encapsulating a cytokine in SUVs, due to the small size of SUVs, they have a long circulating time and can reach the tumor without accumulating first in the liver, spleen and other lymphoid tissues. Thus, even if Kedar suggests the use of liposomes for the delivery of cytokine, it only suggests the use of **small unilamellar liposomes** which would exert a quite different biological effect than that obtained by the method of the present invention.

In addition, the synergistic effect obtained by the combination of the liposomal chemotherapy and MLV-encapsulated cytokine is not taught or suggested by the combination of these two publications.

To briefly summarize, Kedar does not show quite what the rejection alleges, and even if the combination were obvious, it (the combination) would not reach the claimed subject matter. In other words, the combination, even if obvious, would not result in the use of MLVs as claimed.

Applicants respectfully request withdrawal of the rejection and allowance of all the claims on the merits.

Respectfully submitted,

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